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Genetic studies of bipolar disorder in patients selected by their treatment response*

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SUMMARY

Bipolar disorder (BD) is a major mood disorder with several genes of moderate or small effect contributing to the genetic susceptibility. It is also likely heterogeneous, which stimulated efforts to refine its clinical phenotype, studies investigating the link between BD susceptibility and response to a specific mood stabilizer appear to be one of the promising directions.

In particular, excellent response to lithium prophylaxis has been described as a clinical marker of a more homogeneous subgroup of BD, characterized by an episodic course, low rates of co-morbid conditions, absence of rapid cycling, and a strong genetic loading. These results also suggest that lithium response clusters in families (independent of the increased familial loading for affective disorders), likely on a genetic basis.

For almost 40 years, clinical studies have pointed to differences between lithium responders (LR) and non-responders (LNR). For instance, there is a higher frequency of BD in LR families. As well, investigations in offspring of LR and LNR probands show that the offspring of LR tend to manifest a higher frequency of affective disorders, less co-morbidity and an episodic course of the disorder, compared with the offspring of LNR, who had a broad range of psychopathology, a higher rate of co-morbidity and a chronic course of the disorder.

A number of candidate genes have been studied in patients treated with lithium; of these, several showed an association in at least one study: cAMP responsive element binding protein (CREB), X-box binding protein 1 (XBP-1), inositol polyphosphate-1-phosphatase (INNP1), serotonin transporter gene (5-HTT), brain-derived neurotrophic factor (BDNF), phospholipase γ-1(PLCγ-1), dopamine receptors (D2 and D4), polyglutamine tracts, tyrosine hydroxylase, inositol monophosphatase (IMPA), mitochondrial DNA, and breakpoint cluster region (BCR) gene.

Clinical studies have shown as well that the treatment response and outcome appear to be specific for the different types of mood stabilizers. Patients who respond to lithium exhibit qualitative differences from patients responding to other medications, such as valproate, carbamazepine or lamotrigine. Responders to carbamazepine had atypical clinical features, such as mood-incongruent psychosis, an age at onset of illness below 30 years old, and a negative family history of mood disorders. Similarly, in a study comparing the phenotypic spectra in responders to lithium versus lamotrigine the probands differed with respect to clinical course (with rapid cycling and non-episodic course in the lamotrigine group) and co-morbidity, with the lamotrigine-responder group showing a higher frequency of panic attacks and substance abuse.

In conclusion, pharmacogenetic studies may provide important clues to the nature of bipolar disorder and the response to long term treatment.

Key words: Lithium response, pharmacogenetic, probands.

RESUMEN

El trastorno bipolar (TB) es un trastorno afectivo con varios genes, de efecto leve o moderado, que contribuyen a su susceptibilidad. Es asimismo un trastorno heterogéneo, lo que ha estimulado diversas iniciativas para refinar el fenotipo de los pacientes con este trastorno. Particularmente en el TB, una respuesta excelente a la profilaxis con litio ha sido descrita como un marcador clínico en un subgrupo más homogéneo en TB, caracterizado por un curso episódico, baja prevalencia respecto a comorbilidad, ausencia de ciclado rápido y una carga genética importante. En relación con ello, y a pesar de que la totalidad de los estudios no coinciden, la mayor parte sugiere que seleccionar «probandos» de acuerdo con su respuesta al tratamiento incrementa la homogeneidad fenotípica. Estos resultados sugieren asimismo que la respuesta al litio «se agrupa» en familias (independientemente de la tasa familiar incrementada para trastornos afectivos), muy probablemente con bases genéticas.

Por casi 40 años, los estudios clínicos han dilucidado las diferencias entre los respondedores a litio (LR) y los no respondedores (LNR). A este respecto, existe una frecuencia más alta de TB en familias LR; asimismo, las investigaciones en los descendientes de los probandos LR y LNR han demostrado que los descendientes de LR tienden a manifestar una mayor frecuencia de trastornos afectivos, menor comorbilidad, y un curso episódico del trastorno comparados con los descendientes de LNR, quienes muestran un amplio espectro de psicopatología, una alta tasa de comorbilidad, y un curso crónico del trastorno.

Diversos genes candidatos han sido estudiados en pacientes tratados con litio, y varios de ellos han mostrado una asociación en al menos un estudio: proteína de unión al elemento de respuesta (cAMP, *responsive element binding protein*, CREB), proteína de unión a X-box 1 (*X-box binding protein* 1, XBP-1), inositol polifosfato-1-fosfatasa (INNP1), transportador de serotonina (5-HTT), factor de crecimiento

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derivado del cerebro (*brain-derived neurotrophic factor*, BDNF), fosfolipasa γ-1(PLCγ-1), receptores dopaminérgicos (D2 y D4), poliglutamina, tirosina hidroxilasa, inositol monofosfatasa (IMPA), DNA mitocondrial y el gen BCR.

Los estudios clínicos han demostrado que la respuesta al tratamiento y el pronóstico parecen ser específicos para los diferentes tipos de estabilizadores del ánimo. Los pacientes que responden al litio exhiben diferencias cualitativas respecto a los pacientes que responden a otros estabilizadores del ánimo, como valproato, carbamazepina o lamotrigina. Los respondedores a carbamazepina presentan características clínicas atípicas, como psicosis incongruente con el afecto, una edad de inicio del trastorno menor a 30 años de edad y no cuentan con historia familiar de trastornos afectivos. Finalmente, un estudio entre los respondedores al litio y los respondedores a lamotrigina demostró que los probandos difieren con respecto al curso clínico del trastorno (con ciclado rápido y un curso no episódico en los pacientes que responden a lamotrigina), así como en la comorbilidad, teniendo los pacientes que responden a lamotrigina una mayor frecuencia de crisis de angustia y abuso de sustancias.

En conclusión, los estudios farmacogenéticos podrían proveer de hallazgos importantes respecto a la naturaleza del trastorno bipolar y la respuesta al tratamiento a largo plazo.

Palabras clave: Respuesta al litio, farmacogenética, probandos.

GENETIC STUDIES OF BIPOLAR DISORDER IN PATIENTS SELECTED BY THEIR TREATMENT RESPONSE

Bipolar disorder (BD) is a major mood disorder with an important genetic contribution to its etiology.[1,2] The currently accepted genetic model of BD is that of oligogenic inheritance with several genes of moderate or small effects contributing to the genetic susceptibility. Some of the chromosomal regions supported by more than one study are those in 4p, 12q24, 13q, 18p11, 18q and 22q.[3,4] However, many of these findings are not consistent for a variety of reasons, including methodological differences, ascertainment schemes, and markers genotyped.

Bipolar disorder is likely heterogeneous, which stimulated efforts to refine its clinical phenotype. These include classification of affected subjects based on their clinical characteristics, such as the presence of co-morbid conditions, specific symptoms, especially psychosis, and response to treatment. In particular, studies investigating the link between BD susceptibility and response to a specific mood stabilizer appear to be a promising direction; hence, the focus of this review will be to describe the pharmacogenetic characteristics associated with a specific response to a mood stabilizer.

LITHIUM

Phenotypic characterization of responders to lithium

Excellent response to lithium prophylaxis has been described as a clinical marker of a more homogeneous subgroup of BD, characterized by an episodic course,[5] low rates of co-morbid conditions,[3] absence of rapid cycling,[6] and a strong genetic loading.[7-9] Not all, but most studies of lithium response suggest that selecting probands according to treatment outcome increases phenotypic homogeneity. These results also suggest that lithium response clusters in families (independent of the increased familial loading for affective disorders), likely on a genetic basis.[10] Likewise, several studies elucidated the increased rates of affective disorders among relatives of primary affective disorder probands using the outcome on lithium treatment as a discriminatory criterion.[11,12] Several reports indicated also a relatively simple model of inheritance, in some cases compatible with a major-gene effect in lithium responders (LR).[8,9]

For almost 40 years, clinical studies have pointed to differences between LR and non-responders (LNR), with reproducible findings in LR probands and their relatives, as described in table 1. Although clinical methods to evaluate lithium response differ between research groups, findings paint a consistent picture. Specifically, there is a higher frequency of BD in LR families,[11,13-15] as well as a higher prevalence of unequivocal response to lithium in relatives of LR probands;[16-18] conversely, a higher frequency of schizophrenic spectrum disorders has been reported in the LNR families.[19,20] Other studies have as well reported the association between the episode sequence and lithium response. Specifically, a predominant pattern of mania-depression-free interval (MDI) has been positively associated with lithium response.[6,21]

However, family history studies are not unequivocal; some could not find any difference between lithium responders and non-responders[22,23] found an inverse association between family history and lithium response.[24,25] The smaller number of discrepant findings, as pointed by Alda,[26] could be related to different methodologies, particularly in the definition of lithium response and non-response, and the changing trends in the diagnosis of mood disorders.[27]

Studies in offspring of bipolar parents and lithium response

Investigations in offspring of LR and LNR probands are consistent with family and family history studies. More than 20 years ago, McKnew's[28] findings on the offspring of BD patients supported the association between lithium response in the parents and in the offspring. More recent

Table 1. Clinical/genetic studies of response to prophylactic lithium

Reference	n	Sample description	Outcome evaluation	Results
Mendlewicz et al.[15]	36	24 R/ 12 NR	BD and UD FH rates	BD FH higher in R (15/24)
Aronoff et al.[19]	18	7 R / 5 NR	FH of suicide, major affective disorder or hospitalization	Positive FH higher in R (70%) than in NR (20%)
Maj et al.[17]	100	59 R / 41 NR	FH of major psychoses, affective psychoses and BD	Positive FH of BD higher in R (32%) than in NR (21%)
Misra et al.[25]	79	70 R / 9 NR (only NR were studied)	FH of affective disorders	Over 70% had FH of affective disorder
Prien et al.[106]	91	48 R / 43 NR	Reduction of episode frequency	FH higher in R (88%)
Mendlewicz et al.[18]	22	16 R / 6 NR	BD FH rates	Over 80% of R had at least one 1st or 2nd degree relative with BD
Smeraldi et al.[11]	145	92 R / 53 NR	Rates of affective disorders in first-degree relatives	Higher in relatives of R, compared to NR
Grof et al.[14]	121	71 R / 50 NR	Rates of BD and schizophrenia in first-degree relatives	Higher BD rates in R; higher rates of schizophrenia in NR
Sautter et al.[20]	218	76 R / 142 NR	Rates of affective disorders and schizophrenic spectrum disorders in first-degree relatives	Higher morbid risk of schizophrenic spectrum disorders in NR
Coryell et al.[22]	186	Morbidity on lithium: Low: 62; Medium 55; High 69	FH and symptomatology under lithium treatment	BD FH was not associated with a better outcome for probands under lithium
Engstrom et al.[24]	98	47 FH / 51 NFH; 81 R / 17 NR	Lithium response according to FH and AAO	Poorer response associated with FH of BD and earlier AAO
Dunner et al.[23]	96	52 R / 44 NR	Relapse rate under lithium treatment	Lack of association between FH and lithium prophylaxis
Grof et al.[16]	64	24 bipolar relatives of bipolar R probands	Lithium response scores in relatives of R and NR	Higher prevalence of unequivocal response in R relatives
Abou-Saleh et al.[13]	27	27 BD	Affective Morbidity Index (AMI) during lithium treatment	Lower AMI in patients with FH of affective disorder (BD, UD)
McKnew et al.[28]	6	6 offspring of LR patients	Lithium response in BD and offspring	Parents and offspring were concordant with lithium response
Duffy et al.[29]	36	21 R / 15 NR	Psychopathology in the offspring of R and NR	Offspring of R tend to manifest affective disorders, with few co-morbidity and an episodic course
Duffy et al.[30]	55	34 R / 21 NR	Psychopathology and clinical course in the offspring of LR and NR	Offspring of R showed good premorbid functioning and manifested classical mood disorders with an episodic course
Kruger et al.[94]		9 BD, 9 healthy siblings	Changes in rCBF	Decreased rCBF in MFC in BD; increased for siblings in the same region. Changes in the DLPFC and RAC, distinguishing valproate- from lithium-responsive patients
Duffy et al.[31]	15	12 R / 3 NR	Offspring response to mood stabilizer and parents' clinical profile	R offspring derived from R families; lithium response in the offspring was associated with an episodic course

R: Responders; PR: Partial responders; NR: No responders; BD: Bipolar disorder; UD: Unipolar disorder; AAO: Age at onset; FH: Family history; NFH: No family history; MZ: Monozygotic; DZ: Dizygotic; NA: non applicable.

studies have confirmed these findings; for instance, Duffy and colleagues[29] studied the offspring of 13 LR probands (n=21), and the offspring of 10 LNR probands (n=15). Her findings show that the offspring of LR tend to manifest a higher frequency of affective disorders, less co-morbidity, and an episodic course of the disorder, compared with the offspring of LNR, who had a broad range of psychopathology, a higher rate of co-morbidity, and a chronic course of the disorder. A prospective study in this high-risk population showed as well that among the LR offspring there was no occurrence of schizoaffective disorders, and confirmed the association between parental course of the disorder and lithium response in the offspring.[30] In addition, another study from the same group suggested

that treatment response in the affected offspring is associated with treatment response in the affected parent.[31]

In summary, family studies suggest that LR are genetically distinct from LNR, and that their disorder appears to have a stronger genetic basis,[32] findings that have also been supported by studies of age at onset and LR[24,33] (Ortiz et al., in preparation). Nevertheless, the response to treatment could be influenced by a separate genetic factor, independent of the predisposition to the illness itself, as suggested from the findings of Turecki, hypothesizing that the locus on chromosome 15 may be involved in the etiology of BD, whereas the locus on chromosome 7 may be related to the response to lithium treatment.[34]

Molecular genetic studies in patients treated with lithium

A number of studies examined specific candidate genes and response to lithium; typically, these genes have been selected based on possible mechanism of action. However, most of the pharmacogenetic studies have yielded conflicting results (table 2).

a) *cAMP responsive element binding protein (CREB)*: A transcription factor that increases the expression of key growth factors involved in synaptogenesis and neurogenesis, has been proposed as a target in the study of BD, due to its role in gene expression. An association study by Mamdani et al[35] compared 180 LR, 69 LNR, and 127 controls. The researchers reported an association between lithium response and CREB1-1H SNP (G/A change) and the CREB1-7H SNP (T/C change). The CREB1 gene has as well been associated to recurrent depression in women suggesting the existence of a sex-specific susceptibility gene that could interact with nuclear estrogen receptors.[36,37]

b) *X-box binding protein 1 (XBP-1)*: The transcription factor X-box binding protein (XBP-1) was first identified by its ability to bind to the x-box, a conserved transcriptional element in the human leukocyte antigen (HLA) DR alpha promoter. XBP-1 is upregulated as part of the endoplasmic reticulum (ER) stress response. It has been found recently that the 116C→G polymorphism causes an impairment of the ER stress response and increases the risk of BD,[38] while there have been reports regarding the association between the -116C/G SNP pf the XBP1 gene and lithium prophylaxis in BD.[39] Taken together, these studies suggest the association of a lower XBP1 expression and lack of response to lithium.[26]

c) *Inositol polyphosphate-1-phosphatase (INNP1)*: INPP1 encodes the enzyme inositol polyphosphate-1-phosphatase, one of the enzymes involved in phosphatidylinositol signaling pathways, which has been studied with respect to the therapeutic action of lithium. In fact, the study from Steen[40] in a Norwegian sample showed that 67% of lithium responders showed the C937A polymorphism, compared with 11% of non-responders, although some other studies have not replicated these findings.[41]

d) *Serotonin transporter gene (5-HTT)*: One of the most studied genes of BD,[42,43] being the most commonly investigated polymorphism the insertion/deletion polymorphism in the promoter region. With regard to lithium response, conflicting results have been obtained, in the sense that previous studies have reported that the short allele variant is associated with a poor response to lithium,[44-46] although other studies have indicated the opposite association.[47]

e) *Brain-derived neurotrophic factor (BDNF)*: BDNF is a neurotrophic factor implicated in neuronal proliferation and synaptic plasticity. Conflicting results regarding an association between BD and BDNF have been reported,[48,49] although in other studies rapid cycling has been associated with Val66met polymorphism of BDNF.[50] In lithium responders, Rybakowski et al.[51] studied 88 BD patients, stratified by lithium response as excellent, partial or non-responders. His findings support the association of Val/Met genotype of Val66Met polymorphism with excellent responders, as well as a possible interaction between this genotype and the serotonin transporter in lithium responders,[52] although studies with larger samples have contradicted these initial findings.[53] This could probably be related to differences in the ascertainment of lithium response.

f) *Phospholipase γ-1(PLCγ-1):* Lithium is thought to stabilize mood by acting at the phosphoinositide cycle, and the γ-1 isozyme of phospholipase C plays an important role in the phosphoinositide second messenger system. Therefore, polymorphisms in the PLCγ-1 gene have been investigated in lithium responders. The study by Turecki et al.[54] involved over 130 patients, and found an association between lithium response and the PLC γ-1/5 polymorphism. Although his findings have been replicated by other groups,[55] other studies have failed to replicate the initial findings.[56]

g) *Dopamine receptors (DR) D2 and D4*: The DRD2 gene, localized at 11q22.3-q23,[57] and the DRD4 gene,[58] located near the telomere of chromosome 11p,[59] are candidates for prediction of lithium response in mood disorders. However, most studies in lithium-responsive patients have not confirmed the initial positive findings.[60,61]

h) *Polyglutamine tracts*: Family studies showing anticipation and RED studies indicating that bipolar patients have longer CAG repeats have suggested that trinucleotide repeats may play a role in the etiology of BD.[62-64] However, a recent replication study from previous findings did not support the association with triple repeat expansion in ERDA1 and CTG18.1.[65] Two

Table 2. Molecular genetic studies in patients treated with lithium

Reference	Sample description	Target	Result
Tyrosine hydroxylase			
Cavazzoni et al.[71]	48 BD and 6 UD	Tyrosine hydroxylase gene	No association
Inositol monophosphatase (IMPA)			
Steen et al.[107]	21 BD	(IMP) gene A1	No association
Shamir et al.[72]	56 LR / 11 NR	IMP in lymphoblastoid cell lines	Low IMP activity in lithium responders
Dimitrova et al.[79]	42 LR / 35 NR	IMPA2	No association
Sjoholt et al.[78]	16 LR / 16 NR	IMPA1 and IMPA2	No association
PLCγ-1			
Turecki et al.[54]	136 BD LR	PLCγ-1	Positive association for PLCγ,-1/5 polymorphism
Ftouhi-Paquin et al.[56]	133 BD	PLCγ-1	No association
Lovlie et al.[55]	29 LR / 16 NR / 16 unclassified or PR	PLCγ-1	Association with PLCγ,-1/8 polymorphism
INPP-1			
Steen et al.[40]	23 BD	INPP 1	Positive association for C937A SNP
Michelon et al.[41]	61 R / 49 NR BD	INPP-1, 5HTT, BDNF, AP-2β, GSK-3β	No association
Dopamine receptors			
Serreti et al.[60]	43 BD, 12 MDD	DRD3	No association
Serreti et al.[61]	100 BD and 25 UD	DRD2, DRD4, GABRA1	No association
5-HTT			
Del Zompo et al.[47]	67 BD	5-HT transporter	L-allele associated with non-response
Serreti et al.[45]	167 BD and 34 MDD	5-HT transporter	Homozygosity for s allele associated with worse response
Rybakowski et al.[44]	67 BD	5-HT transporter	Higher frequency of s allele in NR
Polyglutamine tracts			
Turecki et al.[108]	70 BD LR	Polyglutamine tracts	No evidence of polyglutamine expansions
Turecki et al.[109]	138 BD LR	CAG repeats	No association
BDNF			
Rybakowski et al.[51]	27 ER / 44 PR / 17 NR	BDNF gene	Positive association for lithium-responders and Val66Met BDNF polymorphism
Masui et al. [53]	110 LR / 51 LNR	BDNF gene	No association
Rybakowski et al.	31 ER / 54 PR / 26 NR	BDNF genes and 5-HTT interaction	S patients with Val/Val genotype were more frequently no responders; Val/Met or Met/Met genotype was more frequent among responders
XBP1 gene			
Masui et al.[39]	43 R / 23 NR	-116 C/G SNP of the XBP1 gene	Lithium treatment is more effective among BD patients with the -116 C allele carrier
Kakiuchi et al.[38]	2 pairs of MZ twins discordant for BD and one pair of healthy twins	Gene related to ER stress response (XBP1)	-116C→G polymorphism of XBP1 associated with an increased risk for BD. Only valproate ameliorated the ER stress response compromised by the risk allele, not lithium nor carbamazepine
CREB genes			
Mamdani et al.[35]	180 R / 69 NR BD	CREB genes	Association with CREB1-1H and CREB1-7H SNP
Other genes			
Alda et al.[110]	174 BD, 176 UD, 98 SCZ	MN blood group	Association and Hardy-Weinberg disequilibrium
Turecki et al.[85]	138 BD	Monoamine oxidase A	No association
Serreti et al.[86]	90 BD and 18 MDD	TPH 1	No association
Duffy et al.[87]	138 BD	GABrA3, GABrA5, GABrB3	No association
Serreti et al.[88]	102 BD, 22 MDD	5-HT2A, 5-HT2C, 5-HT1A	No association
Alda et al.[89]	138 BD	CRH and PENK genes	No association
Turecki et al.[34]	106 BD (247 total)	Complete genome scan using 378 markers	Possible linkage to 15q14 (etiology?) and 7q11.2 (response to lithium treatment?)
Serreti et al.[84]	160 BD and 41 MDD	COMT, MAOA, Gβ3	No association
Sun et al.[111]	12 BD, 8 controls	Lithium-regulated genes in cultured lymphoblasts	A1B-AR gene expression is higher in lithium responders
Szczepankiewicz et al.[90]	89 BD	T-50C polymorphism of GSK-3β	No association
Masui et al.[83]	43 R / 118 NR	BCR gene	Lithium treatment may be less effective in patients homozygous for the Ser796 allele
Turecki et al.[112]	55 BD	Five chromosome 18 markers and Golf gene	No association
Turecki et al.[113]	68 BD (170 total)	Four chromosome 18 markers	No association

BD: Bipolar disorder; UD: Unipolar disorder; MDD: Major depressive disorder; SCZ: Schizophrenia; R: Responders; NR: No responders; ER: Excellent responders; PR: Partial responders; NR: No responders; PLCγ: Phospolipase gamma; GABr: GABA receptor; BNDF: Brain-derived growth factor; rCBF: regional cerebral blood flow; MFC: Medial frontal cortex; DLPFC: Dorsolateral prefrontal cortex; RAC: Rostral anterior cingulated; SNP: single nucleotide polymorphism; XBP1: X-box binding protein 1; ER: Endoplasmic reticulum.

studies involving lithium-responsive patients did not confirmed either the association.[66,67]

i) *Tyrosine hydroxylase* (TH): Tyrosine hydroxylase is an oxidase that converts tyrosine to L-hydroxyphenylalanine (L-DOPA). This enzyme is rate-limiting for the synthesis of both dopamine and norepinephrine; and the TH gene has been localized to the short arm of chromosome 11 (11p15). The cumulative evidence available to date regarding linkage studies of chromosome 11 markers and bipolar disorder report no association between the TH gene and BD.[68-71]

j) *Inositol monophosphatase (IMPA)*: The activity of IMPA, the target enzyme of lithium in the phosphatidilinositol (PI) signal transduction system, has been another candidate for the study of lithium response, and studies have shown a lower activity of IMPA in cells lines from lithium-responsive patients.[72] Two genes coding for IMPA, IMPA1 and IMPA2 have been identified; the first is localized to chromosome 8q21.13-21.3[73] and the second in the chromosomal region 18p11.2. Whereas no linkage or association studies have provided so far evidence for a role of IMPA1 in BD, there have been many reports suggesting the role of 18p11.2 as a susceptibility locus for the disorder;[74-77] none of the studies investigated patients selected by their lithium response, though. There are two association studies that did included this criteria: the one from Sjoholt,[78] which reports an apparent significant association between IMPA2 and BD; however, the one from Dimitrova[79] did not find any significant association between LR and IMPA2.

k) *Mitochondrial DNA*: Mitochondrial dysfunction has been implicated in the physiopathology of BD, based in findings related to abnormal brain energy metabolism, increased levels of 4977-bp deletion in mitochondrial DNA, and co-morbidity of affective disorders in certain types of mitochondrial disorders;[80] the association of mitochondrial DNA (mtDNA) 5178 and 10398 polymorphisms with BD has been reported as well.[81] Recently, in a study involving 34 lithium responders and 20 non-responders, Washizuka reported the association between mtDNA 10389A polymorphism and lithium response;[82] however, more studies are needed to confirm this association.

l) *Other candidate genes:* Having conducted a complete genome scan in 247 individuals, the study from Turecki et al.[34] suggested that a locus on chromosome 15 (15q14) may be involved in the etiology of the disorder, whereas the locus on chromosome 7 (7q11.2) may be involved in lithium response.

A recent study from Masui[83] has as well implicated the breakpoint cluster region gene (BCR), which is located on chromosome 22q11, and lithium response. The study, that included 43 LR and 118 LNR, showed that lithium treatment might be less effective in patients homozygous for the Ser796 allele of the BCR gene than in patients with the Asn796 allele; in addition, it showed that the same variant associated with the illness was associated with a poorer outcome, which raises the possibility of an association between BCR Ser796 and a more severe illness presentation.

Although most of the following studies have not been replicated, the following gene variants did not appear to be associated with lithium outcome in BD: MAO A,[84,85] TPH,[86] Gamma-Aminobutyric Acid (GABA) receptors (A3, A5, B3),[87] serotonin receptors (5HT2A, C, and 1A),[88] CRH and PENK genes,[89] Catechol-O-methyl transferase (COMT),[84] Glycogen synthase kinase 3 (GSK-3β),[90] and PREP.[91]

OTHER MOOD STABILIZERS

Clinical studies have shown that the treatment response and outcome appear to be specific for the different types of mood stabilizers. Specifically, patients who respond to lithium exhibit qualitative differences from patients responding to other medications, such as valproate, carbamazepine or lamotrigine.[3] In addition, treatment response could be a specific characteristic of individual patients, i.e., patients responding to carbamazepine or valproate had evidence of prior nonresponse to lithium.[92,93]

Using positron emission tomography, Kruger and colleagues[94] analyzed the changes in regional cerebral blood flow (rCBF) after induction of transient sadness in euthymic LR (n=9) and nine healthy siblings, and compared them to the results from nine valproate-responsive bipolar patients. Among their findings, the group reports changes specific to the bipolar subgroup in the dorsolateral prefrontal cortex and rostral anterior cingulated that distinguished valproate- from lithium-responsive patients. Also, the results yielded an insight on the changes in the medial frontal cortex that distinguished both lithium- and valproate-responsive patients from healthy siblings.

VALPROATE

Several studies suggest common biochemical pathways for lithium and valproate, including the extracelullar signal-regulated kinase systems;[95] particularly for valproate, alterations in the Na+ channel subunit mRNA levels and MARCKS expression have been reported.[96]

Valproate has been effective in the prophylaxis of rapid cycling and ultra-rapid cycling bipolar disorders; as well as in the acute treatment of mania and mixed states.[93,97,98] Other studies have reported a good antimanic response to

valproate associated with decreasing or stable episode frequencies, and nonpsychotic mania.[99] However, in a naturalistic observation study that included 120 BD patients, responders to valproate had higher rates of psychosis.[100] Among other variables studied, a recent study from Reeves[101] including 20 participants (6 lithium-responsive and 14 valproate-responsive) showed that specific EEG abnormalities, such as sharp activity, could predict response to valproate.

Molecular studies with valproate, although scarce in comparison with those including lithium, have started to show the implications of genes essential in the endoplasmic reticulum (ER) stress response signalling. For instance, the study from Kakiuchi et al.[38] used DNA microarray analysis of lymphoblastoid cells derived from two pairs of twins discordant with respect to BD, and they found downregulated expression of genes related to the ER response in both affected twins. The study shows thus that the 116C→G SNP of X-box binding protein 1 (XPBP-1) causes an impairment of the ER stress response, and was significantly associated with BD. Their results illustrate as well the differential effect of the mood stabilizers on this cascade, specifically, that valproate administration significantly ameliorates the ER stress response compromised by the risk allele -116G by reinforcing ATF6 upstream of the XBP1 loop, while lithium and carbamazepine did not.

CARBAMAZEPINE

Clinical studies have reported that, unlike lithium responders, patients who respond to carbamazepine had atypical clinical features, such as mood-incongruent psychosis;[102] as well as an age at onset of illness below 30 years old.[33] Furthermore, rapid cycling and a negative family history of mood disorders may be associated with a good response to carbamazepine.[92]

The multicenter Study of Long Term Treatment of Affective and Schizoaffective Psychosis (MAP study) was a prospective study with an observation period of more than two years, trying to compare the differential efficacy of lithium and carbamazepine.[103] The study included 171 BD patients: 86 were randomized to lithium and 85 to carbamazepine. All data consistently suggested that lithium was more efficacious than carbamazepine in the maintenance treatment of BD 1 patients, and in those patients with «classical features», i.e., bipolar I patients without mood-incongruent delusions and without psychiatric co-morbidity.

On the contrary, patients with non-classical features responded more favourably to carbamazepine, as there was an inverse association between the number of non-classical features and hospitalization rate for patients under treatment with carbamazepine.

LAMOTRIGINE

A study comparing the phenotypic spectra in responders to lithium versus lamotrigine showed that the probands differed with respect to clinical course (with rapid cycling and non-episodic course in the lamotrigine group) and co-morbidity, having the lamotrigine-responder group a higher frequency of panic attacks and substance abuse. Family history was also an important predictor, that is, relatives of lamotrigine responders had a higher prevalence of schizoaffective disorder, major depression, and panic attacks.[104] Other studies comparing lamotrigine and gabapentin have found that lamotrigine appeared more effective in patients with fewer medication trials, whereas gabapentin appeared most effective in those with younger age and lower baseline weight.[105]

CONCLUSIONS

Recent progress in pharmacogenetic studies has revealed the promissory future of genetic studies according to treatment response, providing a better framework for the understanding of bipolar disorder. However, the main challenge in this realm comprises the integration of genetic, molecular, cognitive and clinical domains, in order to refine the study of the broad spectrum of clinical presentations that can be found in bipolar disorder. Treatment response appears as an invaluable tool for a better understanding of such a complex disorder.

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